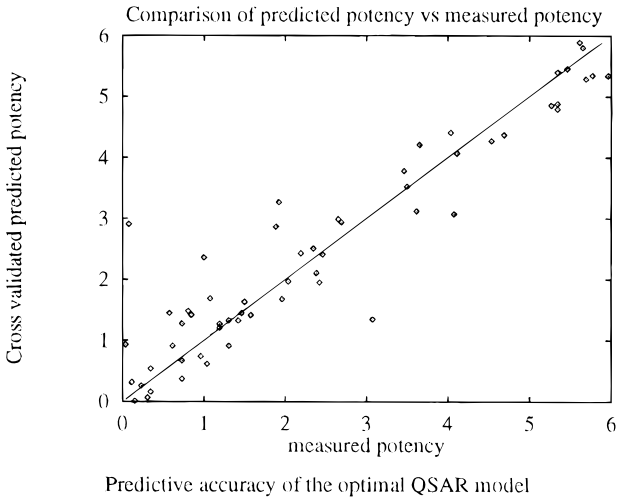


Fig. 1. Predictive accuracy of the optimal QSAR model.

because the covariance scales are much less dependent on the sequence alignment. Model predictions of potency of the compounds in the training set are shown in Fig. 1. Predictions were generated using leave-one-out cross-validation. The logarithmic potency scale used here measures average activity against the panel of bacteria. A unit increase in potency represents a two-fold reduction in the geometric mean MIC.

New sequences were generated by a combinatorial search algorithm. At each round all possible single mutation analogues were evaluated using the best QSAR model. Initially the most potent peptides were used as seeds, those with the highest predicted potencies being used in subsequent rounds. New peptides generated by this process have been assayed and shown to have high potency. A more detailed description of the search algorithm and the results obtained is given in Mee *et al.*[10]

REFERENCES

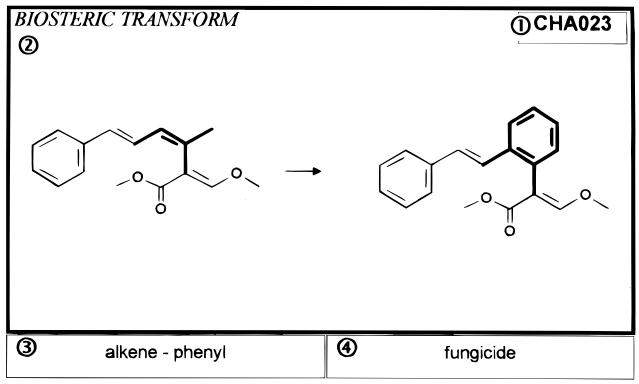
1. Boman, H. G., Wade, D., Boman, I. A., Wåhlin, B. & Merrifield, R. B., Antibacterial and antimalarial properties of peptides that are cecropin-melittin hybrids. *FEBS Letts.*, **259** (1989) 103–6.
2. Andreu, D., Ubach, J., Boman, A., Wåhlin, B., Wade, D., Merrifield, R. B. & Boman, H. G., Shortened cecropin A melittin hybrids. *FEBS Letts*, **296** (1992) 190–4.
3. Wade, D., Andreu, D., Mitchell, S. A., Silvera, A. M. V., Boman, A., Boman, H. G. & Merrifield, R. B., Antibacterial peptides designed as analogs or hybrids of cecropins and melittin. *Int. J. Peptide Protein Res.*, **40** (1992) 429–36.
4. Merrifield, R. B., Juvvadi, P., Andreu, D., Ubach, J., Boman, A. & Boman, H. G., Retro and retroenantio analogs of cecropin-melittin hybrids. *Proc. Natl. Acad. Sci. USA*, **92** (1995) 3449–53.
5. Merrifield, E. L., Mitchell, S. A., Boman, H. G., Andreu, D. & Merrifield, R. B., D-enantiomers of 15-residue cecropin A-melittin hybrids. *Int. J. Peptide Protein Res.*, **46** (1995) 214–20.
6. Skagerberg, B., Hellberg, S., Sjöström, M. & Wold, S., Peptide quantitative structure–activity relationships, a multivariate approach. *J. Med. Chem.*, **30** (1987) 1126–35.
7. Norinder, U., Theoretical amino acid descriptors. Application to bradykinin-potentiating peptides. *Peptides*, **12** (1991) 1223–7.
8. Baroni, M., Clement, S., Cruciani, G., Kettaneh-Wold, N. & Wold, S., D-optimal designs in QSAR. *Quantitative Structure Activity Relationships*, **12** (1993) 225–31.
9. Wold, S., Jonsson, J., Sjöström, M., Sandberg, M. & Rannar, S., DNA and peptide sequences and chemical processes modelled by principal components analysis and partial least squares projections to latent structures. *Anal. Chim. Acta*, **277**, (1993) 239–53.
10. Mee, R. P., Auton, T. R. & Morgan, P. J., Design of active analogues of a 15-residue peptide using D-optimal design, QSAR and a combinatorial search algorithm. *J. Peptide Res.*, **49** (1997) 89–102.

BIOSTER—A Database of Structurally Analogous Compounds

István Ujváry

Plant Protection Institute, Hungarian Academy of Sciences, PO Box 102, H-1525 Budapest, Hungary

To aid the discovery of new drugs and agrochemicals, a compilation of critically selected molecule pairs with similar structures and biological activities is being



⑤
Beautement, K. *et al.*, *Pestic. Sci.*, **31** (1991) 499–519; Kim, B. T. *et al.*, *Biosci. Biotech. Biochem.*, **56** (1992) 624–9; see also Wigerinck, P. *et al.*, *J. Med. Chem.*, **36** (1993) 538–43; Beard, R. L. *et al.*, *Bioorg. Med. Chem. Letters*, **4** (1994) 1447–52.

Fig. 1. Typical data form of *BIOSTER* database with field types as follows: ① ID code; ② structures of the biosteric transformation (biosteric fragments in the analogues are highlighted); ③ chemical fragment types relevant to transformation; ④ biological activity type related to the structures shown; ⑤ key references.

developed for the text and (sub)structure searchable reaction database programs ChemBase™ and ISIS/Base™.[1] In this novel database, named BIOSTER, the representation of a bioanalogue compound pair is similar to that of a chemical reaction in which a reactant is converted to a derivative product, as depicted in typical data form (Fig. 1).

Originally, the database was built upon the idea of bioisosterism, which is one of the most successful techniques of bioactive compound design.[2–6] Recently, however, the selection of structurally similar compounds has been extended beyond bioisosteric analogues. In order to provide the widest possible choice of fragments to practising chemists in their lead generation and optimisation, other structurally and biologically related molecule pairs, such as transition state analogue enzyme inhibitors, pro-drugs, peptide β-turn mimics, etc., are also included. Thus, at least in the context of the present database, the new term bioster(ic) is proposed for structurally similar atomic groups or larger fragments, interchangeable from a biological point of view. (For an elucidative discussion on the terminology of (bio)isosterism, see Ref. 7).

In the database, two structurally analogous molecules containing interchangeable fragments are linked by a hypothetical functional group exchange termed biosteric transformation (i.e. conversion of a lead or prototype compound to its analogue or derivative). Compounds with the same type of biological activity are generally paired chronologically in the database, i.e. the one first reported in the literature is chosen as the progenitor and is on the left side of the transformation. The records also contain textual data fields for the type

TABLE 1
List of Biosteric Fragments Represented in BIOSTER Database

Prototype functionality undergoing transformation	*Number of transformation type in the database*
Acetal	23
Carboxylic acid or acyl group	65
Aldehyde	9
Amine, amide, arginine, etc.	134
Azo or azide	8
Benzene or phenyl	16
Boron	2
Carbamate	16
Chain-to-chain or chain-to-ring	166
Epoxide	5
Ester	72
(enol)Ether or peroxide	22
Halogen	8
Hydrogen or hydroxy	24
Imine or imide	18
Indole, etc.	10
Ketone	33
Methyl, methylene or methine	35
Nitrile or nitro	13
Peptide	183
(Di)phenol	18
Phosphate, phosphonate, etc.	67
Platinum	1
Pyridine or pyrrole	23
Quinone	5
Ring-to-chain or ring-to-ring	472
Sulfate, sulfonamide, etc.	24
Thiol, thioamide, (thio)urea, etc.	41

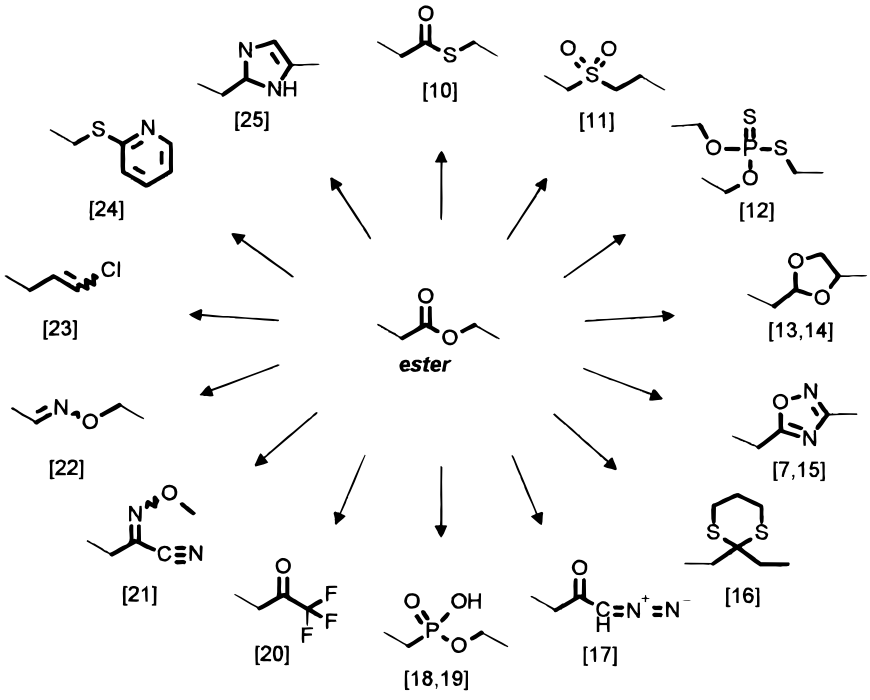


Fig. 2. Selected biosteric fragments for simple carboxylic acid esters and illustrative references (in brackets).

of biological activity related to the particular analogue pair shown and for the interchangeable structural fragments. A data field lists typical literature sources, generally starting with the reference where the application of the biosteric replacement shown in the form was disclosed. The analogue pairs were selected by detailed analysis of primary and secondary literature on medicinal and pesticide chemistry as well as bio(organic) chemistry published up to early 1995. Patents are not considered. It should be pointed out that retention of biological activity in the new derivative was not a criterion for inclusion into the database, since a particular replacement failing in one biological system could work well in others.

Although developed independently, BIOSTER shares several features with the recently described EMIL system[8,9] that automatically generates a variety of potential lead compounds using a database of bioisosteric 'structural evolution' rules derived from medicinal and agricultural chemistry.

As of October 1995, approximately 1,510 bioisosteric and related analogue transformations are registered in the database. Table 1 gives the complete list of the typical fragments for which the actual transformation is coded (for example, acetals and carboxylic acids have ID codes beginning with ACE and ACI, respectively).

Figure 2 shows 14 selected key fragments out of the total 72 with code numbers ESTxxx where a carboxylic ester moiety of a compound is replaced by a structurally analogous functionality affording a derivative with similar biological properties. (These and additional ester replacements in the database in which another functionality was modified to an ester group can be retrieved by a textual search in the chemical fragment type field.)

In summary, BIOSTER is a novel, easy-to-use and expandable database that could be helpful in designing new bioactive compounds based on bioisosterism and other structural modification techniques.

Acknowledgement

The preparation of this presentation was partly supported by the Hungarian Scientific Research Foundation (OTKA Grant No. T014343).

REFERENCES

1. ChemBase and ISIS/Base are products of MDL Information Systems, Inc., San Leandro, California, USA.
2. Schatz, V. B., Isosterism and bio-isosterism as guides to structural variations. In *Medicinal Chemistry*, 2nd edn, ed. A. Burger. Interscience Publishers, Inc., New York, 1960, pp. 72–88.
3. Thornber, C. W., Bioisosterism and molecular modification in drug design. *Chem. Soc. Rev.*, **8** (1979) 563–79.
4. Lipinski, C. A., Bioisosterism in drug design. *Annu. Rep. Med. Chem.*, **21** (1986) 283–91.
5. Burger, A., Isosterism and bioisosterism in drug design. *Progress in Drug Research*, **37** (1991) 287–371.
6. Hansch, C. & Leo, A., *Exploring QSAR. Fundamentals and Applications in Chemistry and Biology*. American Chemical Society, Washington, DC, 1995, pp. 515–21.
7. Floersheim, P., Pombo-Villar, E. & Shapiro, G., Isosterism and bioisosterism case studies with muscarinic agonists. *Chimia*, **46** (1992) 323–34.
8. Fujita, T., Concepts and features of EMIL, a system for lead evolution of bioactive compounds. In *Trends in QSAR and Molecular Modeling 92*, ed. C. G. Wermuth. ESCOM, Leiden, 1993, pp. 143–59.
9. Fujita, T., Nishimura, K., Cheng, Z.-M., Yoshioka, H., Minamite, Y. & Katsuda, Y., EMIL, a system for computer-aided structure transformation of bioactive compounds. In *Natural and Engineered Pest Management Agents*, ACS Symp. Ser. **551**, ed. P. A. Hedin, J. J. Menn & R. M. Hollingworth. American Chemical Society, Washington, DC, 1994, pp. 396–406.
10. Shapiro, G., Floersheim, P., Boelsterli, J., Amstutz, R., Bolliger, G., Gammenthaler, H., Gmelin, G., Supavilai, P. & Walkinshaw, M., Muscarinic activity of the thiolactone, lactam, lactol, and thiolactol analogues of pilocarpine and a hypothetical model for the binding of agonists to the m 1 receptor. *J. Med. Chem.*, **35** (1992) 15–27.
11. Büchi, J., Prost, M., Eichenberger, H. & Lieberherr, T., Synthese und analgetische Wirkung einiger 1-Methyl-4-phenyl-piperidin-(4)-alkylsulfone. *Helv. Chim. Acta*, **35** (1952) 1527–36.
12. Colinese, D. L. & Terry, H. J., Phosalone—a wide spectrum organo-phosphorus insecticide. *Chem. Ind.* (1968) 1507–11.
13. Belleau, B. & Puranen, J., Stereochemistry of the interaction of enantiomeric 1,3-dioxolane analogues of muscarone with cholinergic receptors. *J. Med. Chem.*, **6** (1963) 325–8.
14. Karrer, F., Kayser, H., Buser, H. P. & Ramos, G. M., Insect juvenile hormone mimics: A chemical metamorphosis from terpenoid esters to aryloxy-dioxolanes. *Chimia*, **47** (1993) 302–6.
15. Swain, C. J., Baker, R., Kneen, C., Moseley, J., Saunders, J., Seward, E. M., Stevenson, G., Beer, M., Stanton, J. & Watling, K., Novel 5-HT_3 antagonists. Indole oxadiazoles. *J. Med. Chem.*, **34** (1991) 140–51.
16. Adams, T. C., Dupont, A. C., Carter, J. P., Kachur, J. F., Guzewska, M. E., Rzeszotarski, W. J., Farmer, S. G., Noronha-Blob, L. & Kaiser, C., Aminoalkynyldithianes. A new class of calcium channel blockers. *J. Med. Chem.*, **34** (1991) 1585–93.
17. Ujváry, I. & Prestwich, G. D., An efficient synthesis of the crustacean hormone [12-^{3}H]-methyl farnesoate and its photolabile analog [13-^{3}H]-farnesyl diazomethylketone. *J. Labelled Compds Radiopharm.*, **28** (1990) 167–74.
18. Janda, K. D., Benkovic, S. J. & Lerner, R. A., Catalytic antibodies with lipase activity and *R* or *S* substrate selectivity. *Science*, **244** (1989) 437–40.
19. Ha, H.-J., Fungicidal activity of a series of chloroacetylanilidophosphonates. *Pestic. Sci.*, **37** (1993) 289–92.
20. Hammock, B. D., Abdel-Aal, Y. A. I., Mullin, C. A., Hanzlik, T. N. & Roe, R. M., Substituted thiotrifluoropropanones as potent selective inhibitors of juvenile hormone esterase. *Pestic. Biochem. Physiol.*, **22** (1984) 209–23.
21. Bromidge, S. M., Brown, F., Cassidy, F., Clark, M. S. G., Dabbs, S., Hawkins, J., Loudon, J. M., Orlek, B. S. & Riley, G. J., A novel and selective class of azabicyclic muscarinic agonists incorporating an *N*-methoxy imidoyl halide or nitrile functionality *Bioorg. Med. Chem. Lett.*, **2** (1992) 791–6.

22. Brown, M. A. & Casida, J. E., Influence of pyrethroid ester, oxime ether, and other central linkages on insecticidal activity, hydrolytic detoxification, and physicochemical parameters. *Pestic. Biochem. Physiol.*, **22** (1984) 78–85.
23. Kozikowski, A. P., Roberti, M., Johnson, K. M., Bergmann, J. S. & Ball, R. G., SAR of cocaine: Further exploration of structural variations at the C-2 center provides compounds of subnanomolar binding potency. *Bioorg. Med. Chem. Lett.*, **3** (1993) 1327–32.
24. Raddatz, P., Jonczyk, A., Minck, K.-O., Rippmann, F., Schittenhelm, C. & Schmitges, C. J., Renin, inhibitors containing new P_1-P_1' dipeptide mimetics with heterocycles in P_1'. *J. Med. Chem.*, **35** (1992) 3525–36.
25. Whelan, B., Iriepa, I., Gálvez, E., Orjales, A., Berisa, C., Labeaga, A., García, A. G. & Uceda, G., Synthesis, conformational and pharmacological study of new compounds as possible antagonists of the 5HT-3 receptor. *J. Mol. Graphics*, **12** (1994) 73–4.

Turn Mimetics for Peptide Design

Ursula Egner,* Anke Müller-Fahrnow & Emil Eckle

Research Laboratories of Schering AG, D-13342 Berlin, Germany

Peptides play an important role in the regulation of a wide variety of biological functions, acting as hormones, neurotransmitters or inhibitors. Unfortunately, the therapeutic use of synthetic peptides is often hampered by their lack of metabolic stability and their inadequate transport properties. Substantial evidence exists that many peptides adopt a β-turn conformation in their active, receptor-bound form. A replacement of these turns by peptidomimetics can be beneficial to the stability and other properties as compared to the natural peptide. The conformation of a β-turn can be stabilized either by modifications that influence the conformational behaviour of the peptide backbone or side chain (peptide surrogates) or by templates used as a substitute for the β-turn skeleton. In this summary, we present the variety of organic template molecules for β-turn mimics based on a thorough search in the recent literature.

Contrary to our expectations, only 37 β-turn mimetics were found with a literature search in *Chemical Abstracts* up to June 1996 (Fig. 1). The numbering of the templates corresponds to the reference numbering.[1–37] To limit the number of citations, only the most recent publications are given for the templates and, out of many interesting articles concerning β-turns, only a few were chosen.[38–42] The templates are analysed with respect to β-turn classification, activity and structure elucidation via X-ray crystallography, NMR spectroscopy or modelling studies. Work is under way to incorporate the mimetics as easy-to-use building blocks in the library of our modelling software.

* To whom correspondence should be addressed.

One type of loop observed in proteins is the β- or reverse turn (sometimes called β-bend) which changes the direction of two secondary structural elements. The β-turn is defined in terms of four consecutive residues, named i to $i + 3$, with the following properties: (1) these residues do not form a helix and (2) the distance between the Cα atoms of residues i and $i + 3$ is less than 7 Å. There are seven commonly used categories of β-turn classified by the main-chain torsion angles ϕ and ψ of residues $i + 1$ and $i + 2$. The most frequently occurring turns are of types I or II. They are related by a 180° flip of the peptide group between residues $i + 1$ and $i + 2$. Types I′ and II′ are the backbone mirror images of I and II. Each turn type has specific amino acid residue preferences for at least some of the positions because of the stabilizing contribution these residues provide.

We have classified the β-turn mimetics with respect to the turn type they are designed to mimic. One-third of all compounds are proposed to adopt a II or II′ turn type (**1**, **5**, **7**, **8**, **12**, **16**, **21**, **23**, **31**, **32**, **36**) and three are designed to mimic a I or I′ turn (**13**, **28**, **37**). All other compounds can either substitute for several kinds of turn or are intended to achieve a chain reversal. The templates can be categorized as internal or external β-turn mimetics according to the positions of the template atoms, i.e. if they lie within or outside the β-turn skeleton. The majority of compounds (22 templates) are external β-turns, the others resemble either internal mimetics (**9**, **13–15**, **21**, **30–37**) or are difficult to classify (**6**, **25**). We currently analyse the compounds with molecular mechanics and dynamics techniques (Insight & Discover Software, MSI Inc.) on a Siemens supercomputer S200. We investigated, for example, the influence of the stereochemistry of compound **24** at position 3 of the benzodiazepine ring on the proposed turn type (I or II′). One isomer of **24** is a potent inhibitor of the protein farnesyltransferase with an IC_{50} of 0·9 nM.[24] Molecular dynamics revealed that on average only the *S*-isomer of **24** forms a stable β-turn, which, however, does not belong to any of the turn classes described in the literature.

For almost one-third of the suggested turn mimetics no biological data have been published. Fifteen compounds (**1**, **2**, **5**, **8**, **12–14**, **21**, **22**, **24**, **26**, **28**, **29**, **31**, **34**) have been incorporated into potent ligands with a biological activity in the nM range. Eight compounds turned out to be weak or inactive ligands (**6**, **7**, **9**, **15**, **30**, **33**, **36**, **37**). The conformations of most of the compounds have been confirmed by X-ray structure determination (**1**, **9–11**, **16**, **19**, **21**, **23**, **28**, **29**, **35**), NMR spectroscopy (**3–6**, **12**, **13**, **17**, **20**, **22**, **26**, **27**, **30–32**, **34**, **36**) or modelling studies (**7**, **8**, **14**, **24**, **33**, **37**). Surprisingly, to the best of our knowledge, there is only one example (compound **28**) where the predicted and the experimentally determined structure of the protein (thrombin) in complex with the ligand was published.[28]